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Current status of intravesical chemotherapy trials in the EORTC Urological Group. An Overview

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Summary. The EORTC Urological Group is one of the 31 clinical groups and working parties within the European Organization for Research and Treatment of Cancer (EORTC). Intravesical chemotherapy has been used as chemoresection or chemoprophylaxis. Chemoresection has mainly been utilized in phase II studies to demonstrate ablation of existing disease and to study the mechanism of drug action. These studies are usually performed by individual members to obtain relevant information for the preparation of randomized trials. One example is a phase II chemoresection study with 4′-epi-doxorubicin (EPR). The EORTC GU Group extended its phase II trials to study remission in patients with primary carcinoma in situ. A new concept introduced in the prospective, randomized phase III trials includes the evaluation of chemoresection of a marker lesion as a prognostic factor in long-term prophylactic treatment. Chemoprophylaxis in the phase III trials aims to study the disease-free period, the recurrence rate and the long-term survival. So far, a series of five phase III trials, totaling more than 2,000 patients, demonstrated the efficacy of chemoprophylaxis to reduce tumor recurrence rates. The variation in the results of the different trials are due more to the prognostic factors (characteristics of the tumors) than to the related efficacy of the chemoprophylactic drugs. The selection of currently employed drugs, Mitomycin C, Epirubicin and BCG, is based on reported results, lack of toxicity, and drug availability in Europe. The data collected will be of great importance to determine the optimal clinical management of superficial bladder cancer.

Introduction

The great majority of patients with newly diagnosed bladder cancer will present with a tumor confined to the mucosa or lamina propria (TA, Tl, Tis disease). The likelihood of development of invasive disease, except for patients with carcinoma in situ (Tis), is low. However, 50%–70% of these tumors will recur if initial treatment includes transurethral surgery alone. The main rationale for the utilization of intravesical chemotherapy in clinical practice is its proven efficacy to reduce the recurrence rate of these superficial tumors. Its clinical indications as treatment are limited to primary carcinoma in situ and to the response of marker lesions in studies.

This paper gives an overview of prospective, randomized intravesical chemotherapy trials, conducted mainly by the Genito-Urinary-Tract Cooperative Group of the European Organization on Research and Treatment of Cancer (EORTC) and performed over the last decade.

Chemoresection

Superficial bladder cancer

Although the first reports on chemoresection treatment with a caustic agent, silver nitrate, and with a chemotherapeutic drug, thiotepa (TTPA), were published in Europe in 1903 and 1961, respectively [13, 15], we still consider transurethral surgery to be the most appropriate way to treat superficial bladder cancer.

However, a number of studies have demonstrated the efficacy of Mitomycin C (MMC) in the chemoresection treatment of patients with superficial bladder tumors [8]. The long-term follow-up of patients in chemoresection studies, mainly promoted by the National Bladder Cancer Group, indicated that complete tumor destruction seemed to be independent of the grade and stage of the initial primary tumor and was related to a 50% decrease in the development of subsequent tumors as compared to partial responders, as well as a 50% or more decrease in the development of invasive disease [3, 20]. This information is not available for adriamycin (ADM) or epirubicin (EPR), although we know that both drugs are concentrated in superficial bladder cancer tissue [17]. A multicenter phase II trial was organized to evaluate the ablative efficacy of EPR.

Protocol: phase II study to assess the ablative effects of EPR in recurrent, multifocal Ta/Tl bladder tumors with a marker lesion
Study Coordinator: L. Denis, Antwerp
Activated: October 1985
Closed: April 1986
Number of patients entered: 47

Treatment regimen: treatment consisted of removal, by transurethral resection (TUR), of all visible tumor except for one marker lesion, precisely localized and smaller than 1 cm diameter, followed by 8 weekly instillations of 50 mg EPR, and then reassessed with repeat TUR. The prelimi-

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nary results indicate a 50% complete response rate of the marker lesion, as evidenced by the absence of visible tumor, absence of microscopic carcinoma, and negative cytology at the time of the repeated TUR. Necrotic lesions in the histology specimen were recorded as complete response [1]. The final report on ablation is in progress, pending the central pathology report, and all patients are scheduled for long-term follow-up.

As suggested by the marker lesion studies, the response of the marker lesion may turn out to be an important prognostic factor when correlated with the long-term recurrence rate [3, 20], while a repeated TUR of intensively treated lesions may yield fewer recurrences and perhaps better survival [14]. For both reasons it is felt that it is quite ethical to leave a well-defined and precisely located marker in the bladder to assess the response of an intensive intravesical treatment. Two phase II trials with a marker lesion to study the ablative effect of an intensive short-term course of EPR and MMC, respectively, and a phase III trial to compare the prophylactic value of this regimen alone versus the same regimen plus long-term maintenance therapy are ready for activation by the EORTC GU Group.

Recurrent disease in the 2-year follow-up period will be treated by four weekly courses of drug therapy. The long-term maintenance therapy consists of intravesical drug therapy every 2 months for 2 years. End points of the studies are a progression in T category higher than Tl, the occurrence of distant metastases, and local recurrence after 2 years of treatment and follow-up (EORTC 30864).

Carcinoma in situ

Reports of clinical history and therapeutic response in carcinoma in situ of the bladder are often conflicting. This situation created the need for the development of guidelines to determine the presence and extent of Tis in the bladder and to evaluate therapeutic responses [9, 11]. Consensus on the anatomical definition reserves the term carcinoma in situ for flat, nonpapillary, noninvasive malignant epithelium closely resembling that seen in invasive transitional cell epithelium. This will practically reserve this disease entity for grade 3 lesions with a few grade 2 lesions included. The consensus on the clinical aspects required complete response, which includes negative cytology, to evaluate therapy. Intravesical chemotherapy, of course, is indicated in the primary form of carcinoma in situ, and the difficulty in evaluating it is responsible for the conflicting reports in the literature. There is, however, evidence that chemoresection treatment with ADM, MMC, and BCG may lead to long-lasting complete remissions in this disease with extreme benefit to the patient. Even crossover treatment after failure on one drug may bring additional complete responses [2, 5, 8, 19]. In spite of these encouraging results, it should be kept in mind that long-term treatment and close observation remain a necessity. Carcinoma in situ represented only a few patients in the first EORTC phase III studies, and its diagnosis will be an exclusion criterion in the future for randomized prophylactic studies involving papillary carcinoma.

Further EORTC efforts in this field will concentrate on a phase II study coordinated by G. Jakse, Innsbruck, which is designed to define the number of instillations needed to achieve complete remission and to estimate the percentage of patients achieving complete remission and the percentage of complete responders who have recurrences. The treatment regimen includes six weekly BCG instillations with 120 mg BCG, Connaught strain, diluted in 50 ml saline, followed by control cystoscopy and biopsy. This scheme will be repeated a maximum of two times, hoping to induce complete remission. For patients not responding after three cycles, further treatment will be optional.

Chemoprophylaxis

The rationale of chemoprophylaxis is based on the presumption that the high frequency of recurrent tumor is caused either by persistence of the original tumor after endoscopic destruction, new tumor formation, tumor implantation during surgical manipulation, or the progression of unrecognized Tis disease. The instillation of an active chemotherapeutic drug in the bladder, with good penetration into the urothelium but no local and systemic toxicity, would have a favorable cost-versus-benefit relationship for the patient.

EORTC study 30751

This protocol was the first EORTC phase III study carried out by the GU Group and compared the results of TUR alone versus TUR followed by instillations of TTPA or VM 26.
Study Coordinator: C. Schulman, Brussels
Activated: November 1975
Closed: June 1979
Patients entered: 370

Treatment regimen: This study was designed to compare the effectiveness of TTPA (30 mg) and VM 26 (50 mg) versus no therapy after complete removal of primary or recurrent Ta, Tl bladder tumors. The first instillation was given within 1 month of TUR and repeated every week for the first 4 weeks and then once every 4 weeks over 11 months.

Objectives: To compare the disease-free interval, the recurrence rate, and progression of stage and grade between the three treatment arms.

Results. The disease-free interval is defined as the time interval between the TUR at entry and the date of the first positive biopsy of recurrent tumor. The final analysis showed no statistical difference between the three treatment arms. The recurrence rate is defined as the total number of recurrences observed in a group of patients, divided by the sum of months of follow-up from initial TUR to the date of the last information received, multiplied by 100. Study of the recurrence rate yields more accurate results than study of the disease-free interval since it takes all information available for each patient into consideration.

Table 1. Recurrence rate before and during the study. EORTC 30751

Treatment	Recurrence rate before study	Recurrence rate during study
Thiotepa	15.10	8.36
VM 26	9.28	9.18
Control	11.22	12.82

The recurrence rates per treatment arms before and during the study are presented in Table 1. The statistical results showed no difference between the two treatment arms, but there was a significant difference between TTPA and no treatment despite the fact that the recurrence rate of patients before the study was higher in the TTPA regimen [22].

A second analysis [4] assessed the prognostic importance of the number of tumors, prior recurrence rate, size of the largest tumor, histologic grade, age, treatment, and time interval between start of treatment and TUR at entry on study on the recurrence rate. Using multivariate techniques, the three first variables were found to be the most important factors in discriminating subgroups of patients with different prognoses. These results confirmed the heterogeneous nature of these tumors, which may require a more aggressive approach in patients with a poor prognosis. The analysis of a subset composed of British patients suggested a difference in survival between treated and control patients [12]. However, this could not be confirmed by analysis of the whole group. A further analysis of this important aspect is required when more long-term follow-up data become available.

Toxicity. Myelosuppression occurred in 5% (5 of 105) of patients in the TTPA regimen.

Conclusions. The efficacy of TTPA in lowering the recurrence rate of superficial bladder tumor was established, though no difference was demonstrated in time to first recurrence. These results are comparable to a smaller European trial [10]. Multivariate statistical analysis demonstrated that prognostic factors may be of greater importance than therapy in defining the evolution of recurrence and the outcome of the disease.

EORTC study 30782: TTPA versus adriamycin versus cisplatin in recurrent Ta, Tl papillary tumors after complete resection

Study Coordinator: L. Denis, Antwerp
Activated: June 1979
Closed: September 1983
Number of patients entered: 356

Treatment regimen: This study was designed to compare the effectiveness of three drugs: thiotepa, adriamycin and *cis*platin in patients with superficial bladder tumors. Only patients with *recurrent* Ta and Tl tumors were eligible.

Randomization was carried out after TUR, and the first instillation treatment had to be given within 14 days of TUR. Treatment was given every week for the first 4 weeks and then once every 4 weeks for a total duration of one year.

Objectives. To compare the three treatment groups with respect to recurrence rate, time to first recurrence, progression to a higher stage of the disease and toxicity.

Results. There was no significant difference between the three treatment groups with respect to treatment efficacy [23].

Toxicity. The most important side effect was an anaphylactic reaction on CDDP, which consisted of rash and hypotension in 7 of 68 patients. This experience and a similar report in the literature prompted us to drop the CDDP regimen in this protocol [7].

Table 2. Localization of tumor recurrence according to site and time of recurrence. EORTC 30782

Number of patients with follow-up	266
Patients with recurrence	159 (60%)
Patients with recurrence at 3 months	54 (20%)
Patients with recurrence at 3 months at *same* site as initially involved	42 (16%)

Conclusions. The finding that there were no differences in the recurrence rate between the three treatment arms corresponds to another European randomized study where no statistical difference was noted between BCG and TTPA, although in this study the difference between BCG and ADM was significant [6].

The local toxicity of 30782 remained low (5%–10%) and was more prevalent for ADM. However, general toxicity was reported in one case (thrombocytopenia) in the TTPA arm.

A high incidence (16%) of local recurrence at 3 months at the same site as the initial tumor (see Table 2) was observed and prompted us to take into account the possible bias of incomplete resection in our following protocols.

EORTC study 30790: Adriamycin versus epodyl versus TUR only in the management of superficial bladder cancer

Study Coordinator: K. H. Kurth, Rotterdam
Activated: November 1979
Closed: September 1983
Number of patients entered: 443

Treatment Scheme. This study was reserved for patients presenting with primary and recurrent Ta/Tl tumors. The treatment regimen started within 14 days after TUR and compared the efficacy of adriamycin 50 mg versus epodyl 1.13 g versus no treatment. Drug instillations were given every week for 4 weeks and then once every 4 weeks over 11 months for a total of 1 year.

Objectives. To compare the disease-free interval, tumor recurrence rate, and the increase in tumor stage or grade of recurrent tumors.

Results. In 1982, the control arm (TUR alone) was closed to further entry because the tumor recurrence rate was significantly higher after TUR alone than in the patients receiving adjuvant chemotherapy (see Table 3). Patients who had already entered the study in the control group remained in the trial until their first recurrence.

In a recent analysis, patients treated by TUR alone had significantly higher recurrence rates as compared to ADM or epodyl (see Table 4). There is no significant difference between the two treatment arms. However, as expected, the recurrence rate is much lower in primary patients than in patients with recurrent tumor. The most important prognostic factors were the number of tumors at entry on study, the prior recurrence rate, and G category [16].

Table 3. Recurrence rate by treatment group. EORTC 30790

	Adriamycin/ Epodyl	Control
Number of patients randomized	135	71
Number of patients with follow-up	73	47
Number of patients with recurrences	16	22
Percent with recurrences	22%	47%
Total number of recurrences	22	41
Total months of follow-up	755	447
Recurrence rate/100 PTS. months	2.91	9.17
Comparison of recurrence rate	*P Value*	
Adriamycin/Epodyl vs Control	$P < 0.001$	

Table 4. Overall recurrence rate. Mean follow-up 19 months. EORTC 30790

	ADM	Epodyl	Control
N-PTS	163	153	69
With recurrence	63	55	44
N-recurrence	93	81	81
Recurrence rate	2.45	2.21	5.90
ADM VS	Epodyl	NS	
Epodyl VS	Control	$P < .001$	
ADM VS	Control	$P < .001$	

Toxicity. Instillations were stopped because of excessive local toxicity in six patients, three on each treatment. Only mild systemic side effects like nausea and diarrhea were seen after instillation of either adriamycin or epodyl.

Conclusions. This study confirmed the advantages of chemoprophylaxis as determined in the previous EORTC study 30751. Epodyl and ADM are equally effective in chemoprophylaxis. These results are comparable to the results obtained in EORTC 30782 and other randomized trials, where ADM at different doses of 20 and 30 mg, was compared to MMC at a dose of 20 mg (18) and ADM 50 mg versus MMC 20 mg in different treatment schedules, short-term versus long-term prophylaxis.

In the 30790 study, residual tumor was found in 9% of cases on the first control cystoscopy, as compared to 30782 where 16% of patients demonstrated tumor at the original location at the time of first control cystoscopy. It was felt that future randomized studies should focus on the best time for initiation of therapy and that short-term treatment should be evaluated versus maintenance treatment.

EORTC studies 30831 and 30832: Randomized studies to assess the prophylactic value of immediate versus delayed administration of Mitomycin C (MMC 30831) and Adriamycin (ADM 30832) and to assess the value of maintenance treatment versus no maintenance treatment in superficial TCC of bladder

Study Coordinator: 30831 C. Bouffioux, Liège
30832 K. H. Kurth, Rotterdam
Activated: September 1983
Closed to patient entry: February 1986
Number of patients entered: 30831: 524
30832: 448

Treatment regimen. The treatment regimen consists of four weekly instillations of ADM 50 mg or MMC 30 mg, followed by five monthly instillations (total of nine instillations) for a total of 6 months. A second randomization assigns the patient to a further six instillations or no further treatment.

Objectives. To determine if early administration of MMC or ADM after TUR (within 6 h) gives better results than delayed instillation (7–10 days after TUR) and to determine if 6-month treatment gives the same results as 12-month treatment. Results will be analyzed in terms of disease-free interval, recurrence rate, increase in stage of recurrent tumor, and the frequency of side effects.

Results. The period of follow-up is still too short to try to draw any statistical conclusion and the figures may possibly change in the future.

Toxicity

EORTC 30831. A total of 2,896 instillations of MMC were evaluated: 1,426 in the early group and 1,470 in the delayed group. The local toxicity was low and led to the delay of instillation in 4% of patients and stopping treatment in 6 of 325 patients (2%). Early instillations seem to bring slightly more side effects than delayed instillations. The general tolerance was also good with allergic reactions observed in 17 patients (5%).

EORTC 30832. Bacterial cystitis requiring delay of instillation treatment with ADM in the early instillation scheme was reported in 10% as compared to 3% in the delayed scheme. Chemical cystitis requiring a delay or stop occurred in 4% of the patients.

The last prophylactic protocol where primary carcinoma in situ is included concerns EORTC protocol 30845: a comparative study of intravesical instillation of MMC and BCG in primary and recurrent Ta-T1 papillary carcinoma and primary carcinoma in situ

Study Coordinator: F. Debruyne, Nijmegen (joint IKO-IKZ)
Activated: January 1985
Closed to patient entry: October 1986
Number of patients entered: 329

However, only 7 (4%) had Tis disease at entry on study. The first preliminary results will be available in the near future.

Discussion

The EORTC prophylactic phase III trials have shown no differences in efficacy or side effects between thiotepa, adriamycin, or epodyl. Mitomycin C and BCG are under current investigation. In general, more local side effects such as chemocystitis can be expected with ADM, MMC, or BCG while systemic toxicity is more prevalent with BCG and TTPA.

Our two last intravesical trials were initiated to study the questions of treatment timing, immediate versus delayed instillations, and treatment duration, 6 versus 12 months. The answers obtained from these trials will be of tremendous importance in shaping our future research.

Over the various intravesical trials carried out by the EORTC, two prognostic factors have been constantly revealed to be of utmost importance: the number of tumors at entry on study and the patients' previous recurrence rate. The recurrence rate is more than double in multiple as opposed to single tumors, while the recurrence rate of the primary single tumor is only one-third that of recurrent, multiple tumors.

It is clear that the aggressiveness and cost of the treatments studied should be based on a patient's prognosis. This situation necessitates dividing the patients into subgroups according to good or poor recurrence risk. Our present phase III trials with a single tumor randomize between no instillation and single-dose chemotherapeutic instillation following TUR, while patients with multiple tumors will be subjected to intensive treatment over 2 months that can be evaluated on a marker lesion, followed by no further treatment or maintenance treatment.

These studies will contain prospective central pathology since depth of infiltration, grade of differentiation, and concomitant carcinoma in situ are basic anatomical parameters of utmost importance. These factors were essential for prognosis in a prospective randomized trial by the Registry for Urinary Tract Tumors in Aachen [21]. Separate studies will also be carried out in patients with carcinoma in situ, starting with phase II trials to answer basic questions relating to response rate.

Many more concepts regarding optimal treatment of intravesical chemotherapy, such as duration of instillation, dose, volume, pH, and osmolality, are open questions. Few patients with TaTlGl-2 bladder cancer eventually die of the disease and a cost-effective relationship towards a lower tumor recurrence rate is difficult to establish. However, some prospective trials seem to show improved survival, which may largely compensate for the hardship placed on both patients and doctors by strict protocol requirements [14].

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